PARSİYEL MEME IŞINLAMASI

Dr. Yıldız Yükselen Güney

Ankara Onkoloji Hastanesi

Konular

- Akselere parsiyel meme ışınlaması (APBI)
  - **Tanım**
  - Multikateter APBI
  - Tek giriş brakiterapi cihazı ile APBI
  - Eksternal APBI

- IORT Parsiyel meme ışınlaması
  - Tanım
  - TARGIT
  - Elektron

Akselere Parsiyel Meme Işınlaması

Meme koruyucu cerrahi sonrası lumpektomi lojuna 1-2 cm marj ile brakiterapi ya da eksternal ışınlama yöntemleri kullanılarak uygulanan hipofraksiyone radyoterapi

Yaşam Kalitesi

Kısa süreli RT

Neden APBI?

- Hasta konforu
- Sosyoekonomik nedenler
- Kozmetik sonuçlar
- Ulaşım
- Maliyet

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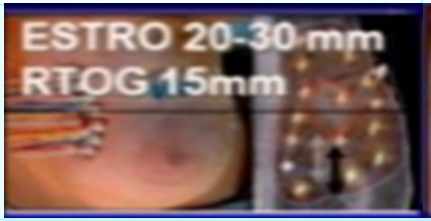
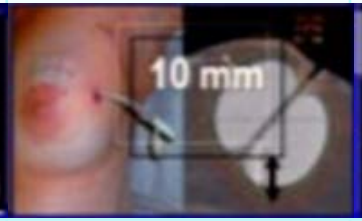
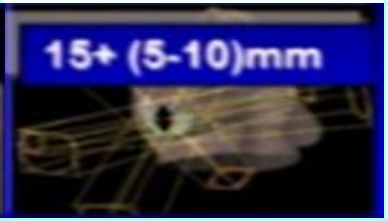
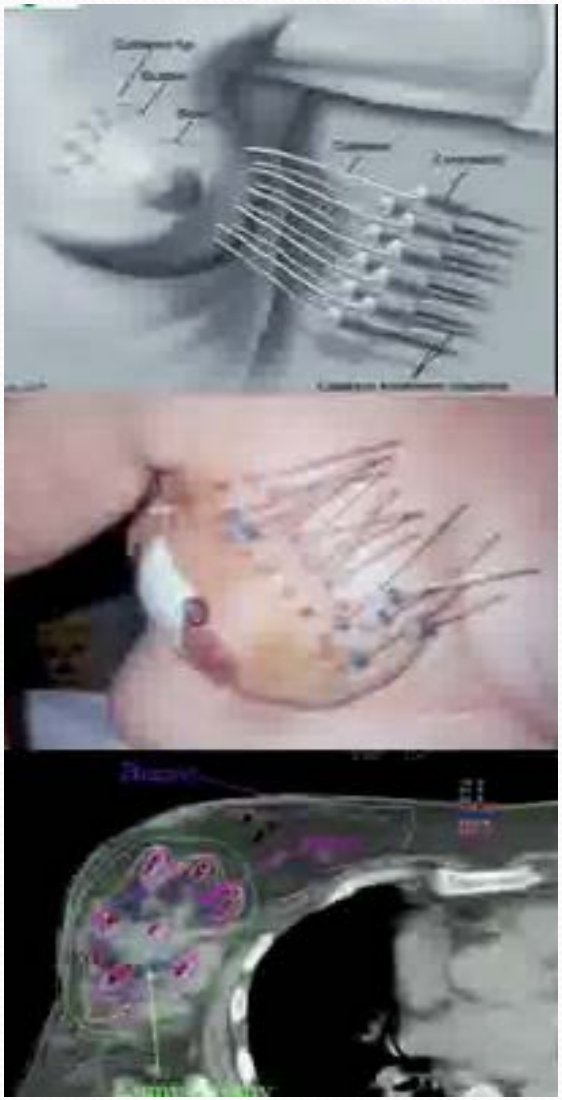
ELIOT 2000-7 1306 hasta	BRACHYTHERAPY MULTI-CATH GEC-ESTRO ‘06 NSABP B39/RTOG ‘413 ‘07	MAMMOSITE ®* 1255 hasta VİRJİNYA ÜNİVERSİTE	3D-CRT-PBI (*) RAPID (OCOG)- IRMA IMPORT (UK) WB40vsPB40vsW+b	TARGIT 50 Kv 1999 Vaidya 2235 hasta
				
Breast 2003	NSABP/RTOG Trial	Keisch IJROBP’03 Vicini et al cancer ‘08	RAPID/IRMA 50 Gy WB+/-boost vs PBI 3.85Gy*10 frk IMPORT WB40vsPBI40vs W36 Gy+b4Gy	
21 Gy*1frk	E.: 4 Gy*8frk/1 hft R.:3,4*10 frk/1-2 hft	3,4*10 frk/1-2 hft	3,85 Gy*10 frk	20 Gy*1frk
$D2\alpha/\beta_{10}$: 54 Gy	ESTRO: 37 Gy RTOG: 38 Gy	38 Gy	44 Gy	50 Gy
$D2\alpha/\beta_{4}$: 87,5 Gy	ESTRO: 42 Gy RTOG: 42 Gy	42 Gy	50 Gy	80 Gy

APBI: İntertisyel Brakiterapi



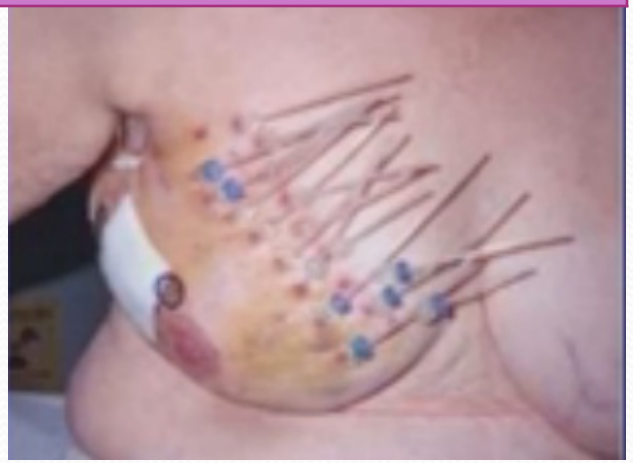
- Lumpektomiden hemen sonra veya ayrı bir seansda uygulanabilir
- USG veya BT kılavuzluğunda kataterler
- RT: lumpektomi kavitesinin 2 cm çevresine
- En uzun takip tek merkezli serilerden
- Deneyimli ellerde mükemmel lokal kontrol

RTOG 95-17

Avantajlar	Dezavantajlar
Düzensiz sınırlı kaviteler	İnvaziv işlem
Deri ve göğüs duvarı koruması	Komplike teknik
Uzun süreli sonuçlar	Kısıtlı ulaşım

%75

- Tekrar multikateter APBI seçimi %94,6
- 12 yıllık takipte % 4 oranında memede rekürrens



Multikateter APBI (HDR/LDR): Özet

Institution	Pt. No.	Median age	F/U mo.	T size (cm) median	N-1 %	ER + %	LR %	Exc/ good Cosm %
Median age 61.7	**T size (cm)** 1.22		**N-1** 7.5%	**ER +** 82%	**LR** 4.6%	**Exc/ good Cosmesis** 88%		
Nat. In. Onc. Budapest *(Polgar)*	45	56 *	133	1.2	2	82	9	78
# U. WI *(Cannon)*	277	~60	61	- [1]	6	89	4.1	-
Wash U *(Garsa)*	151	60	55	- [1]	0	-	3.4	-
Germ-Austrian Multicenter *(Ott)*	274	60.5	63	1.2	0	100	2.9	90
RTOG-9517 *(White)*	99	62	144	1.3	19	75	4	-

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Tek girişli brakiterapi ile APBI

Avantaj	Dezavantaj
Basitleştirilmiş yaklaşım	İnvaziv yaklaşım
Gelişmiş teknolojik erişim	Kavite uyumsuzluk riski
Cerrahın kullanımı	Kısıtlı ulaşılabilirlik

34 Gy 10 frk. 3,4 Gy BID 5-8 gün

Tek girişli brakiterapi ile APBI

Yeni Nesil Cihazlar

Avantajlar;

-dozimetrik sarma

-göğüs duvarı ve cilt koruması

SAVI Ciana Medical

CONTURA Seno Rx

Tek girişli brakiterapi ile APBI: Özet

Institution	Pt. No.	Median age (yr)	F/U mo.	T size (cm) median	N-1 %	ER + %	Local rec %	Exc/ good Cosmesis %
Median age	**T size (cm)**	**N-1**	**ER +**	**LR**	**E-G Cosmesis**			
64	**1.0**	**5%**	**84%**	**2.1%**	**89%**			
U. Pitts (Vargo)	157	62	66	[1] -	2.6	83	2.5	93.5
ASBS Registry (Shah)	1249	65.9	63	1.0	3	87	3.9	90

[#] *Retrospective analysis*

[1] T size > 90% T-1

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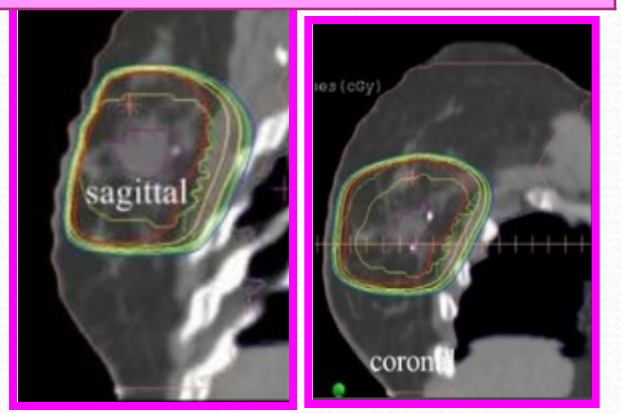
RTOG 0319 Faz I/II 3D CRT APBI

Avantajlar	Dezavantajlar
Non-invaziv	Değişken hedef tanımı
Lineer akseleratörler her yerde	Fraksiyonlar arası ve fraksiyon içi hatalar

- 5 yılda genel memnuniyet %96
- 7 yıllık medyan takipte memede rekürrens %5,7



3D-CRT / IMRT APBI: Özet

Institution	Pt. No.	Median age	F/U mo.	T size (cm) median	N+ %	ER + %	Local recur %	% Exc./ Good Cosmesis
Median age	**T size (cm)**	**N-1**	**ER +**	**LR**	**E-G Cosmesis**			
64	**1.0**	**2 %**	**90%**	**2.2%**	**87%**			
(Berrang)	104	62.6	37	-	0	82	1	82
Esperanza (*Rodriguez*)	51	67	60	1.4	0	96	0	100
US Oncology (*Lei*)	121	62	53	0.95	0	91.7	0.7	98.3
RTOG 0319 (Rabinovitch)	58	61	96	1.0	8	83	6	56

APBI Vaka Profili

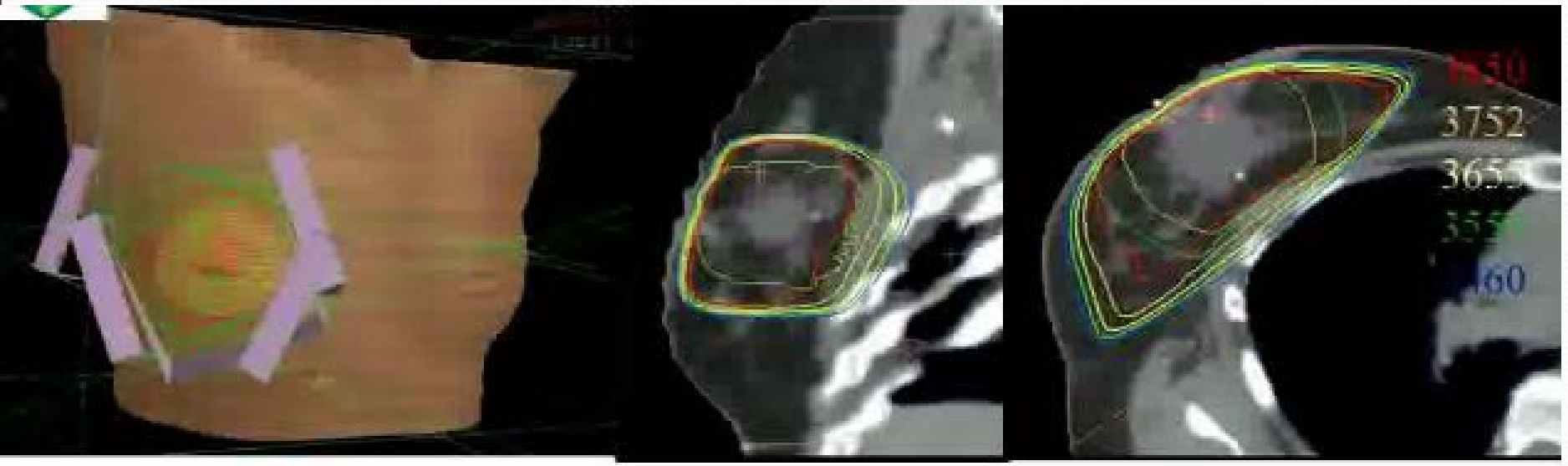
Luminal A Benzeri Meme Kanseri

- Tm boyutu < 20mm
- Lenf nodu negatif
- ER+, PR+, HER2-
- Medyan yaş ≥ 60

APBI Dikkat: Biyoloji

	n	F/ up mo.	Method APBI	Factor	Local Rec %
University WI *(Cannon)*	322	60	MCT	Histopath	12.7
MGH *(Pashtan)*	98	71	3DCRT	TNBC	33
GER-Aust *(Ott)*	274	64	MCT	ER+ but no endocrine therapy	12

APBI: 3DCRT



3 Önemli Faz III çalışma:

- NSABP B39 / RTOG 0413
- RAPID
- IMPORT

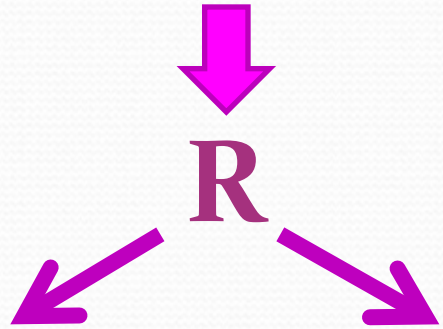
Doz:

3,85 Gy BID x 5 gün

Total : 38,5 Gy

NSABP B-39/ RTOG 0413 FAZ III Çalışma

Lumpektomi ile tedavi edilen evre 0-I,II meme kanserli hastalar:



- WBI 50-50,4 Gy (1,8-2 Gy)
- WBRT+ boost (60-66,6 Gy)

-PBI Mammosite 34 Gy/ 3,4 Gy BID
veya
-Multikateter BRT veya
3D –CRT (38,5 Gy/ 3,85 Gy /BID)

Hedeflenen toplam hasta: 4300

NSABP-B39 /RTOG 0413: 3D APBI kozmetik raporu:

ASCO 2011/ ASTRO 2011 de sadece abstract

- Ortalama izlem 41 ay
- Toksisite ile ilişkili anlamlı olay yok
- 3D - APBI fibrozis, kozmezis, derin konnektif doku toksisiteleri:

  Grade 2: %12

  Grade 3: %3

  Grade 4/5: %0

RAPID çalışması:

- 1°: İpsilateral meme tümör rekürrensi (IBTR)
- 2° : Kötü kozmezis / Radyasyon toksisitesi

WBI N=1065

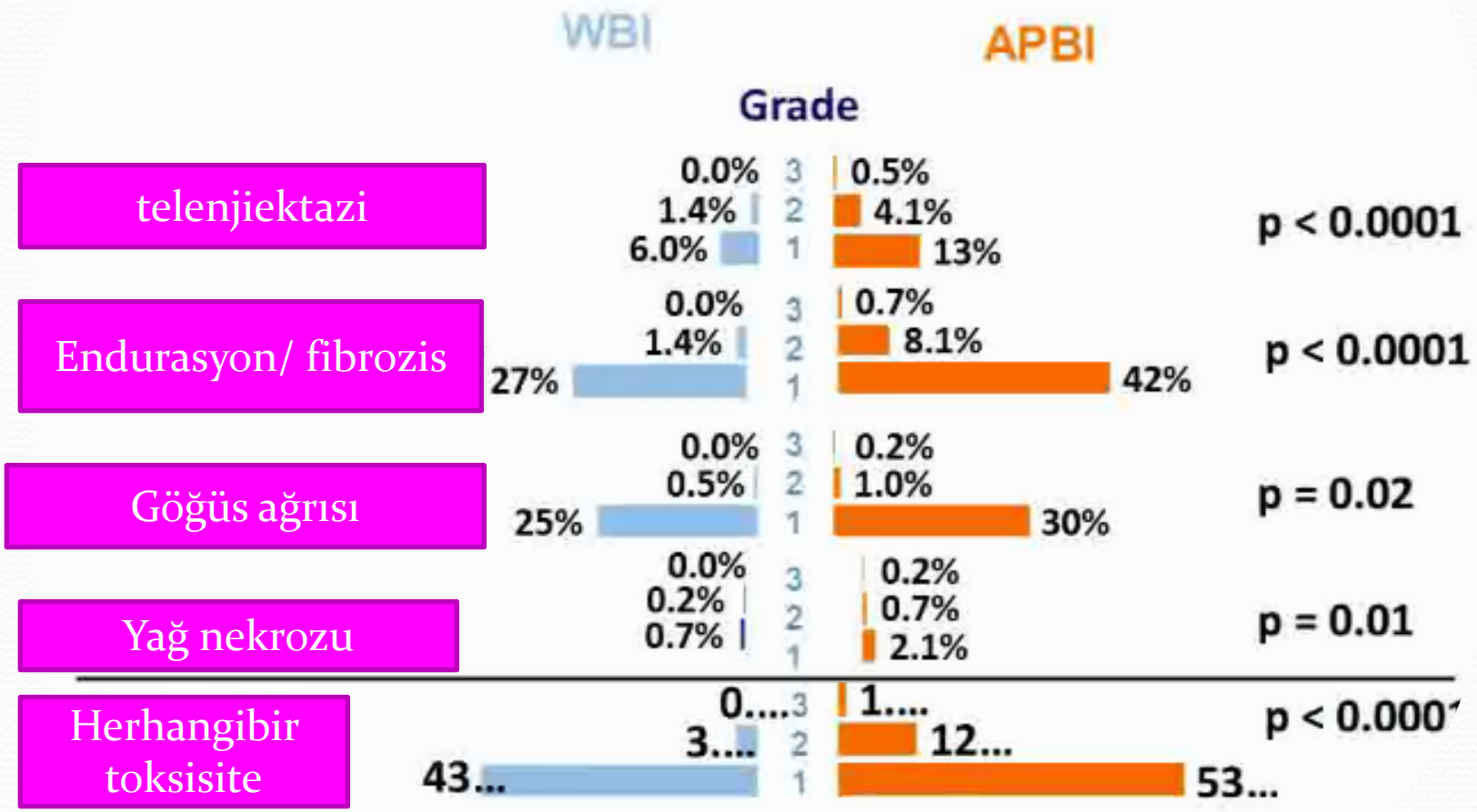
EBRT- APBI
N=1070

Doz 38,5/ 10 Gy BID
(fraksiyonlar arası >6 saat)

- 2 panel (her birinde 3 radyasyon onkoloğu)
- Eğitimden geçmiş, tekrarlayan fotoğraflar alınmış,tedaviye kör
- Geç toksisite, NCI Common Toxicity Criteria For Adverse Events V. 3 ile eğitimli hemşirelerce 1., 3., 5. yılda değerlendirildi.

3 yılda Geç Radyasyon Toksisitesi:

Olivotto, JCO Epub 2013



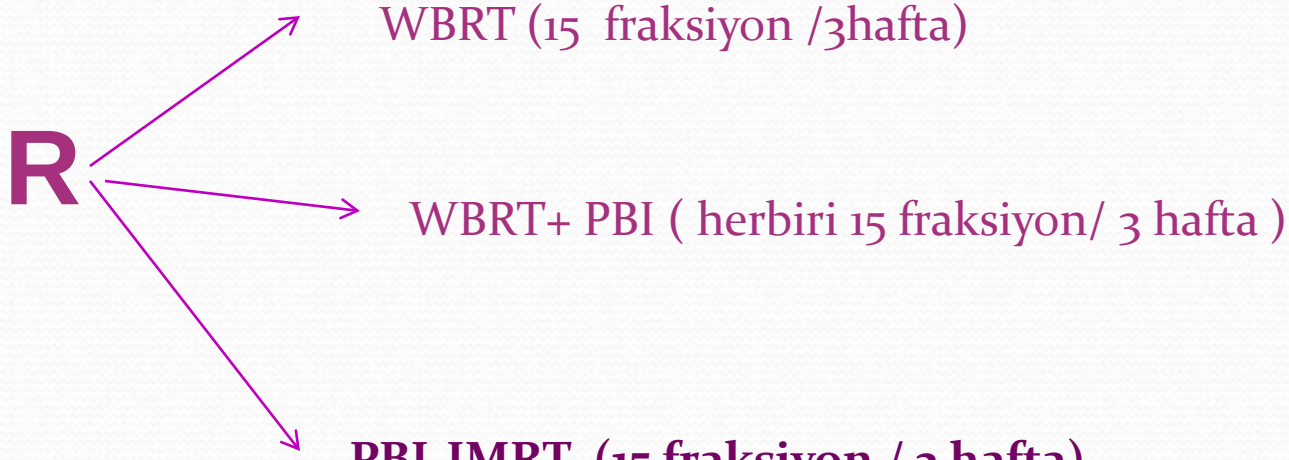
IMPORT Faz III UK Çalışması: PBI- IMRT

kapatılmış, aktif izlem (2006-2010)

Düşük riskli hastalarda APBI_ IMRT yi test etmek için

Primer sonlanım noktası: Lokal kontrol (ipsilateral)

Kriterler:
IDC (ILC Ø)
Pno
LVI (-)
PT<3 cm.
Unifokal
Grade I,II ,III
marjin >2 cm



APBI: Özet

- Biyolojik düşük riskli hastalarda (Luminal A benzeri) APBI'nin uzun süreli ve kabul edilir lokal kontrol oranları gösterilmiştir.

  Evre 1, ER +, >50 yaş

- Diğer meme kanseri türlerine uygulanabilirliğini ve tüm meme ışınlamasıyla etkinlik karşılaştırmasını değerlendirendirebilmek için randomize kontrollü çalışmalara ihtiyaç vardır

- Optimal doz, fraksiyonasyon ve metodolojiler araştırılarak varyasyon azaltılmalı

Konular

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İntraoperatif Parsiyel Meme Işınlaması (IORT)

Cerrahi sırasında, insizyon kapatılmadan önce tümör yatağına tek fraksiyonda yüksek doz (8-21 Gy) radyoterapi verilmesi

IORT

Avantajlar

- Çok lokalize doz uygulanımı
- Tedavi alanının direk görülmesi
- Azalmış hasta yükü
    - EBRT
    - Brakiterapiye bağlı ikincil prosedürlerin olmaması

Dezavantajlar

- Çok lokalize doz
- Son patoloji bilinmiyor
- Gereksiz ted uygulanma olasılığı

Konular

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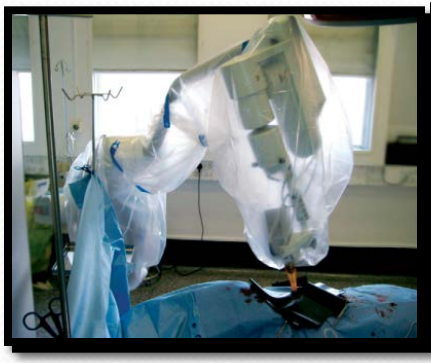
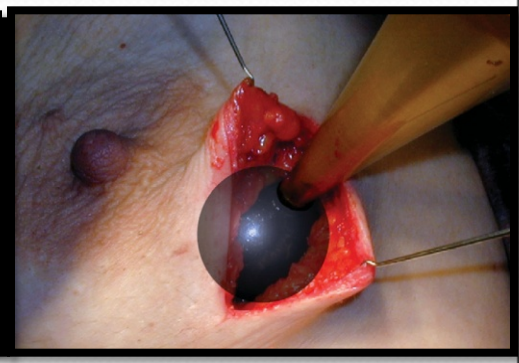
TARGIT-A Çalışması





Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial

Jayant S Vaidya, David J Joseph, Jeffrey S Tobias, Max Bulsara, Frederik Wenz, Christobel Saunders, Michael Alvarado, Henrik L Flyger, Samuele Massarut, Wolfgang Eiermann, Mohammed Keshtgar, John Dewar, Uta Kraus-Tiefenbacher, Marc Sütterlin, Laura Esserman, Helle M R Holtveg, Mario Roncadin, Steffi Pigorsch, Marinos Metaxas, Mary Falzon, April Matthews, Tammy Corica, Norman R Williams, Michael Baum

IORT ± EBRT vs **6-7 hafta EBRT**

Lancet 2010; 376: 91–102

Meme Koruyucu Cerrahi Geçirmiş Hastalar

R

TARGIT –A Grubu

"Intrabeam" ile tek doz "TARGIT"

(grubun %85)

20 Gy yüzey dozu

5-7 Gy 1 cm'de

EBRT Grubu

EBRT

40-56 Gy, 15-25 fx

±

Boost

10-16 Gy, 5-8 fx

TARGIT-A

AMAÇ

- Erken evre düşük riskli, meme koruyucu cerrahi geçirmiş olgularda, IORT' nin konvansiyonel post-operatif RT uygulaması ile karşılaştırılması ("non-inferiority trial")

- **Birincil sonlanım noktası:** Lokal rekürrens

- **İkincil sonlanım noktaları:** Kozmetik, yaşam kalitesi, maliyet-yarar, hasta seçimi, radyobiyoloji çalışmaları

TARGIT-A

Hasta Seçim Kriterleri

- Hasta yaşı ≥45
- Meme koruyucu cerrahiye uygunluk
- Meme irradiasyonu için kontrendikasyon olmaması
- Unifokal, unilateral
- Hastanın takibi uygun olması

TARGIT-A

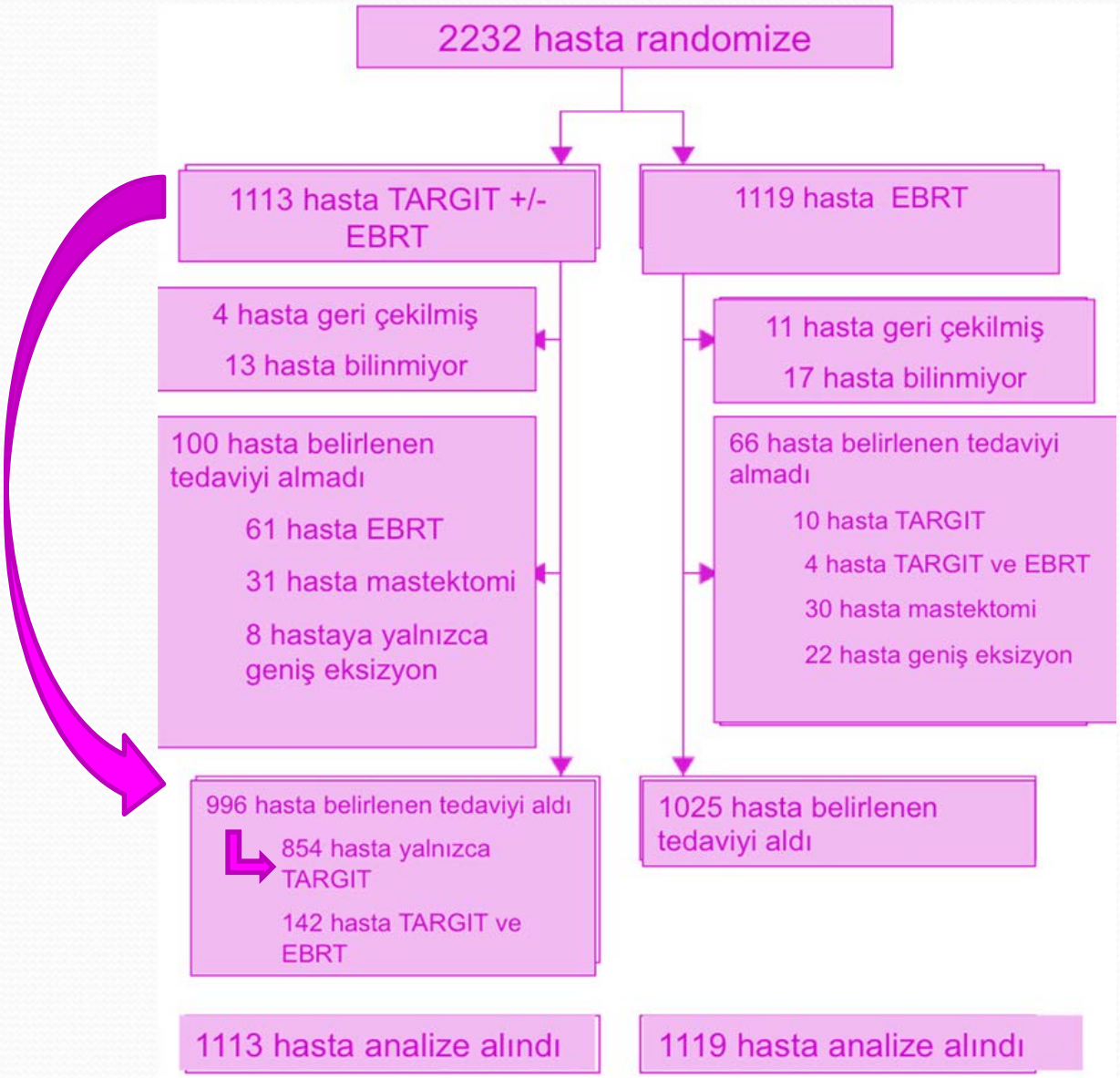
IORT için uygun patoloji

- Unifokal tumor
- <2 cm
- Cerrahi sınır temiz
- İnvaziv duktal karsinoma
- Grade I/II
- EIC (-)
- ER/PR (+)
- Lenf nodu (-)
- PNI (-)

TARGIT-A

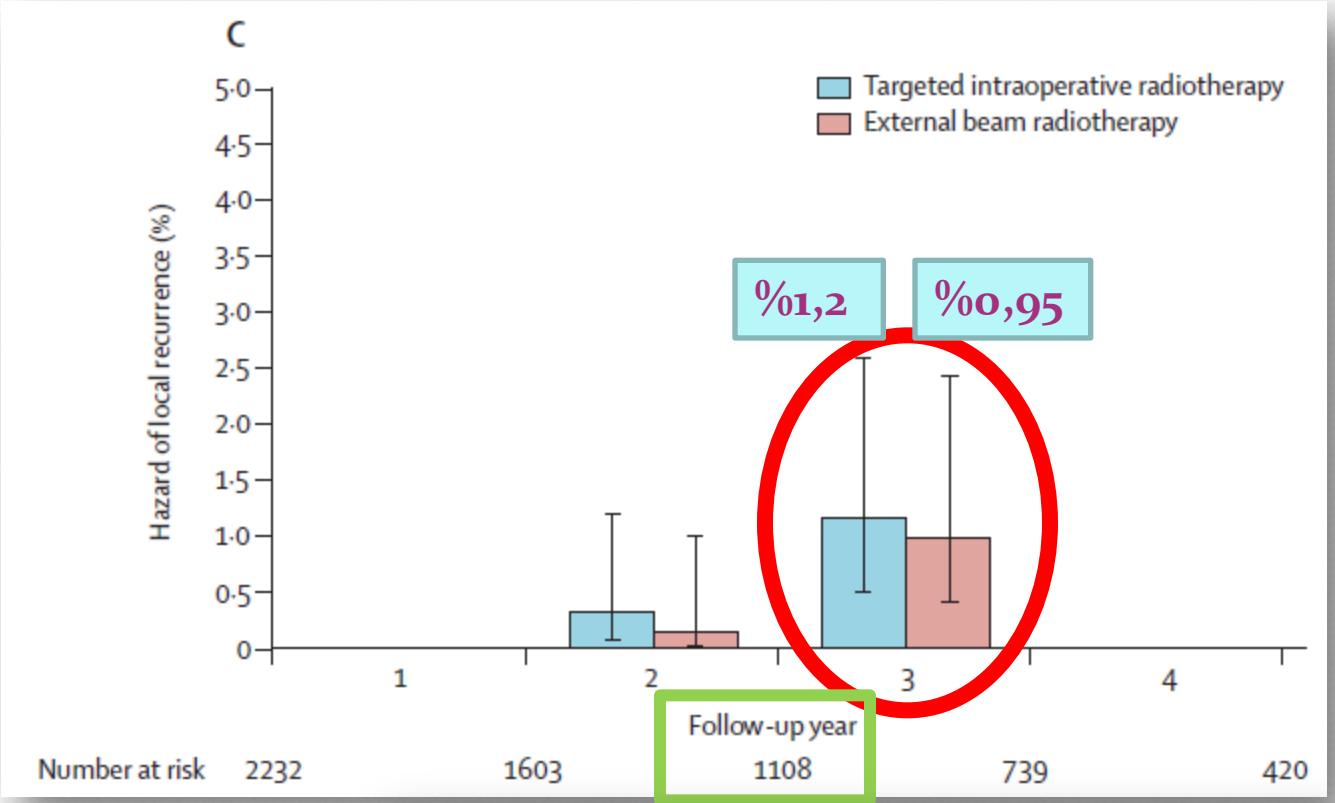
Hasta Dağılımı

	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)
Age (years)		
<45	17/1113 (2%)	10/1119 (1%)
45–54	212/1113 (19%)	167/1119 (15%)
55–64	443/1113 (40%)	464/1119 (41%)
65–74	355/1113 (32%)	381/1119 (34%)
>74	86/1113 (8%)	97/1119 (9%)
Pathological tumour size (cm)		
<1	381/1056 (36%)	388/1061 (37%)
1–2	531/1056 (50%)	519/1061 (49%)
>2	144/1056 (14%)	154/1061 (15%)
Unknown	57/1113 (5%)	58/1119 (5%)
Nodes involved		
0	866/1059 (82%)	898/1070 (84%)
1–3	155/1059 (15%)	149/1070 (14%)
>3	38/1059 (4%)	23/1070 (2%)
Unknown	54/1113 (5%)	49/1119 (4%)
Tumour grade		
1	341/1040 (33%)	374/1048 (36%)
2	540/1040 (52%)	514/1048 (49%)
3	159/1040 (15%)	160/1048 (15%)
Unknown	73/1113 (7%)	71/1119 (6%)


2232 hasta randomize
1113 hasta TARGIT +/- EBRT
1119 hasta EBRT
4 hasta geri çekilmiş
13 hasta bilinmiyor
11 hasta geri çekilmiş
17 hasta bilinmiyor
100 hasta belirlenen tedaviyi almadı
61 hasta EBRT
31 hasta mastektomi
8 hastaya yalnızca geniş eksizyon
66 hasta belirlenen tedaviyi almadı
10 hasta TARGIT
4 hasta TARGIT ve EBRT
30 hasta mastektomi
22 hasta geniş eksizyon
996 hasta belirlenen tedaviyi aldı
854 hasta yalnızca TARGIT
142 hasta TARGIT ve EBRT
1025 hasta belirlenen tedaviyi aldı
1113 hasta analize alındı
1119 hasta analize alındı

TARGIT-A

Lokal Rekkürrens



The local recurrence rate in the targeted intraoperative radiotherapy group was not significantly different from that in the external beam radiotherapy group (1·2% *vs* 0·95%, p=0·41 at 4 years).

TARGIT-A

Komplikasyonlar

	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)	p value
Haematoma needing surgical evacuation	11 (1·0%)	7 (0·6%)	0·338
Seroma needing more than three aspirations	23 (2·1%)	9 (0·8%)	0·012
Infection needing intravenous antibiotics or surgical intervention	20 (1·8%)	14 (1·3%)	0·292
Skin breakdown or delayed wound healing*	31 (2·8%)	21 (1·9%)	0·155
RTOG toxicity grade of 3 or 4†	6 (0·5%)	23 (2·1%)	0·002
Major toxicity‡	37 (3·3%)	44 (3·9%)	0·443

Data are number of patients (%). RTOG=Radiation Therapy Oncology Group. *Some of the patients in the first three rows (haematoma needing surgical evacuation, seroma needing more than three aspirations, infection needing intravenous antibiotics or surgical intervention) could be included in the fourth row (skin breakdown or delayed wound healing). †No patient had grade 4 toxicity. ‡Defined as skin breakdown or delayed wound healing and RTOG toxicity grade of 3 or 4).

Table 5: **Clinically significant complications**

TARGIT-A / Özet

- Komplikasyonlar:

1. RTOG grade 3-4 toksisite EBRT kolunda daha fazla
2. Seroma TARGIT gurubunda daha yaygın
3. Yara iyileşmesi açısından fark yok

- Etkinlik:

1. 4.yıl K-M tahminleri ve yıllık risklere göre TARGIT ve EBRT grupları arasında lokal rekkürrens açısından fark yok.
2. 4. yılda %1,5 sınırla TARGIT için “non-inferiority”

TARGIT Çalışmasına baktığımızda……

- 20 Gy tek dozda

→ etkin
→ yeterli

KONVANSİYONEL EŞ DEĞER YÜZEY DOZU: **70 Gy**

Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alastair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists' group

Summary

Background The TARGIT-A trial compared risk-adapted radiotherapy using single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated external beam radiotherapy (EBRT) for breast cancer. We report 5-year results for local recurrence and the first analysis of overall survival.

Methods TARGIT-A was a randomised, non-inferiority trial. Women aged 45 years and older with invasive ductal carcinoma were enrolled and randomly assigned in a 1:1 ratio to receive TARGIT or whole-breast EBRT, with blocks stratified by centre and by timing of delivery of targeted intraoperative radiotherapy: randomisation occurred either before lumpectomy (prepathology stratum, TARGIT concurrent with lumpectomy) or after lumpectomy (postpathology stratum, TARGIT given subsequently by reopening the wound). Patients in the TARGIT group received supplemental EBRT (excluding a boost) if unforeseen adverse features were detected on final pathology, thus radiotherapy was risk-adapted. The primary outcome was absolute difference in local recurrence in the conserved breast, with a prespecified non-inferiority margin of 2·5% at 5 years; prespecified analyses included outcomes as per timing of randomisation in relation to lumpectomy. Secondary outcomes included complications and mortality. This study is registered with ClinicalTrials.gov, number NCT00983684.

Findings Patients were enrolled at 33 centres in 11 countries, between March 24, 2000, and June 25, 2012. 1721 patients were randomised to TARGIT and 1730 to EBRT. Supplemental EBRT after TARGIT was necessary in 15·2% [239 of 1571] of patients who received TARGIT (21·6% prepathology, 3·6% postpathology). 3451 patients had a median follow-up of 2 years and 5 months (IQR 12–52 months), 2020 of 4 years, and 1222 of 5 years. The 5-year risk for local recurrence in the conserved breast was 3·3% (95% CI 2·1–5·1) for TARGIT versus 1·3% (0·7–2·5) for EBRT (p=0·042). TARGIT concurrently with lumpectomy (prepathology, n=2298) had much the same results as EBRT: 2·1% (1·1–4·2) versus 1·1% (0·5–2·5; p=0·31). With delayed TARGIT (postpathology, n=1153) the between-group difference was larger than 2·5% (TARGIT 5·4% [3·0–9·7] *vs* EBRT 1·7% [0·6–4·9]; p=0·069). Overall, breast cancer mortality was much the same between groups (2·6% [1·5–4·3] for TARGIT *vs* 1·9% [1·1–3·2] for EBRT; p=0·56) but there were significantly fewer non-breast-cancer deaths with TARGIT (1·4% [0·8–2·5] *vs* 3·5% [2·3–5·2]; p=0·0086), attributable to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3·9% (2·7–5·8) for TARGIT versus 5·3% (3·9–7·3) for EBRT (p=0·099). Wound-related complications were much the same between groups but grade 3 or 4 skin complications were significantly reduced with TARGIT (four of 1720 *vs* 13 of 1731, p=0·029).

Interpretation TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected as per the TARGIT-A trial protocol, as an alternative to postoperative EBRT.

Funding University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre, UCLH Charities, National Institute for Health Research Health Technology Assessment programme, Ninewells Cancer Campaign, National Health and Medical Research Council, and German Federal Ministry of Education and Research.

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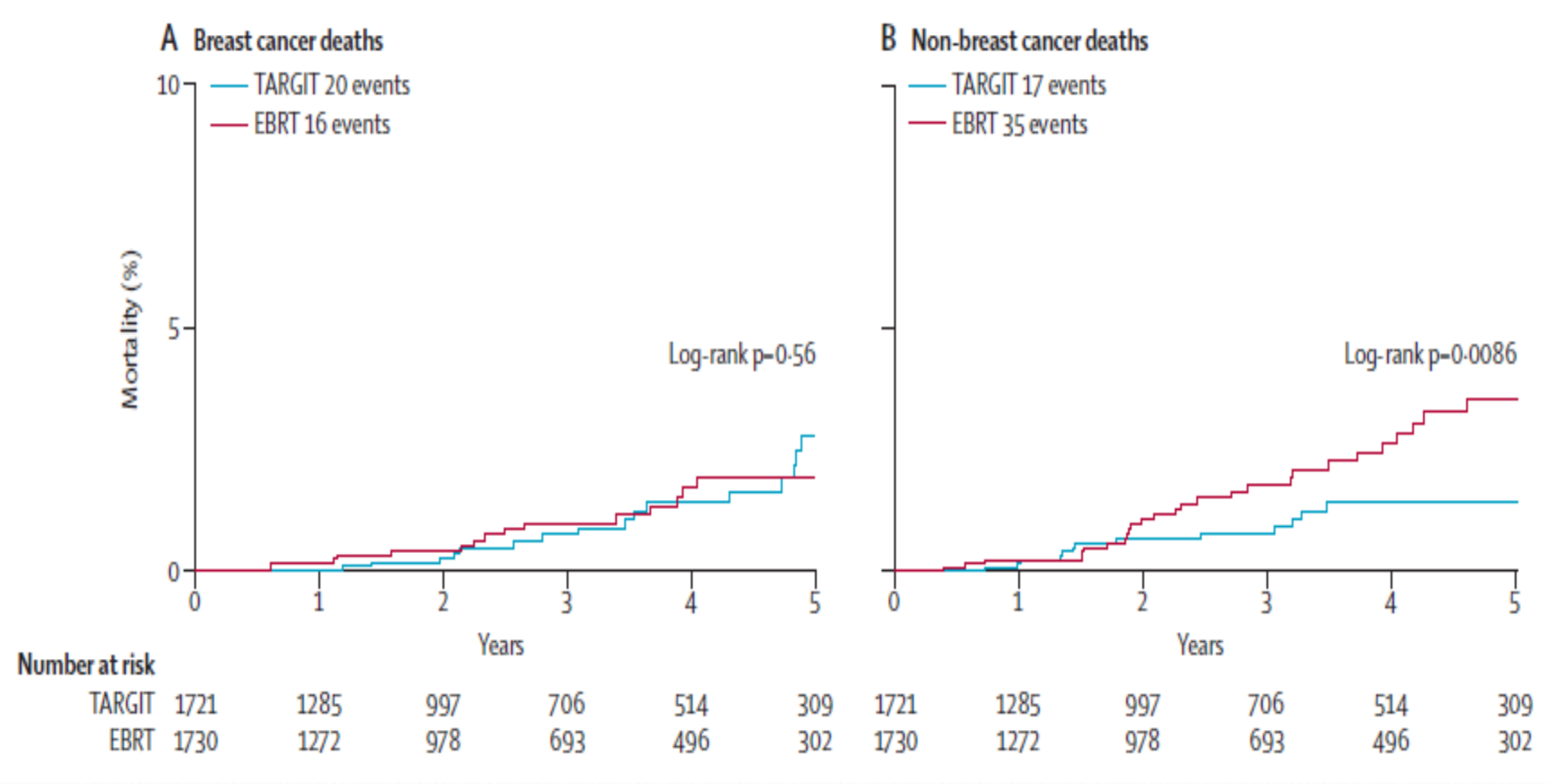
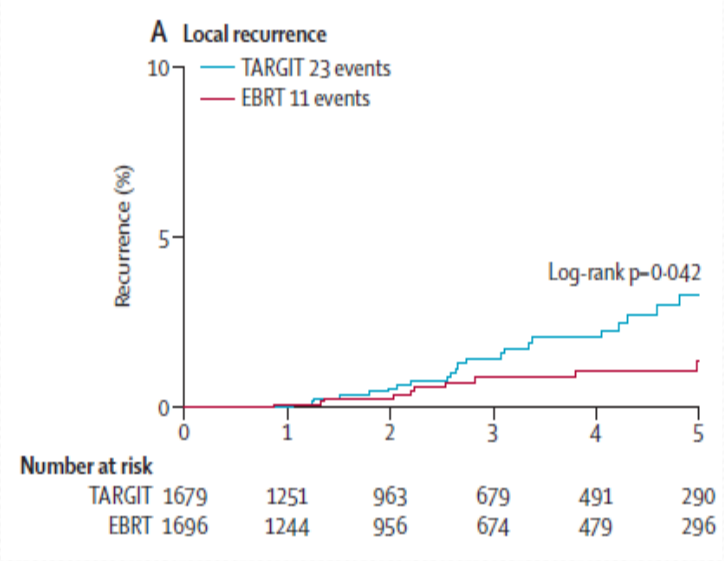
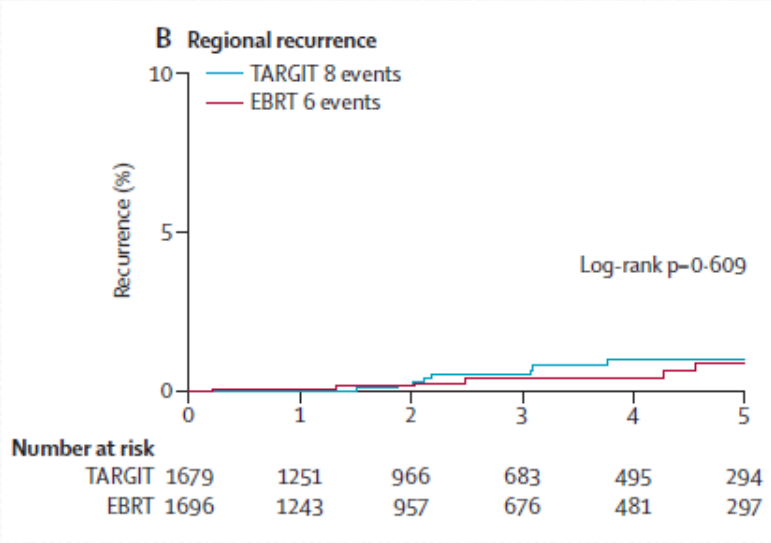
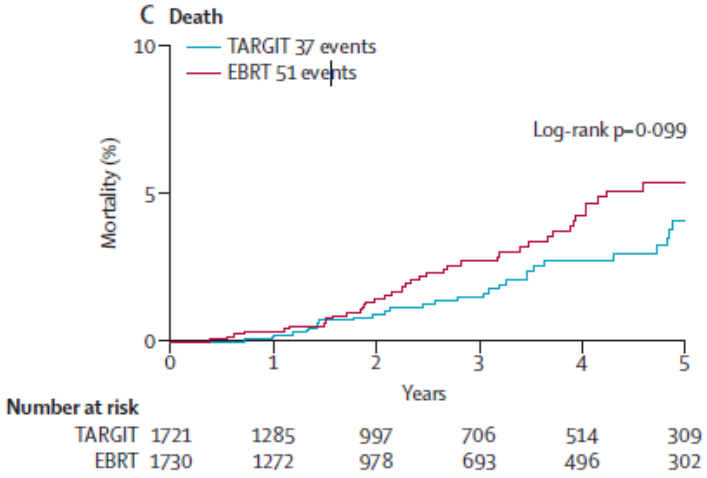
TARGIT

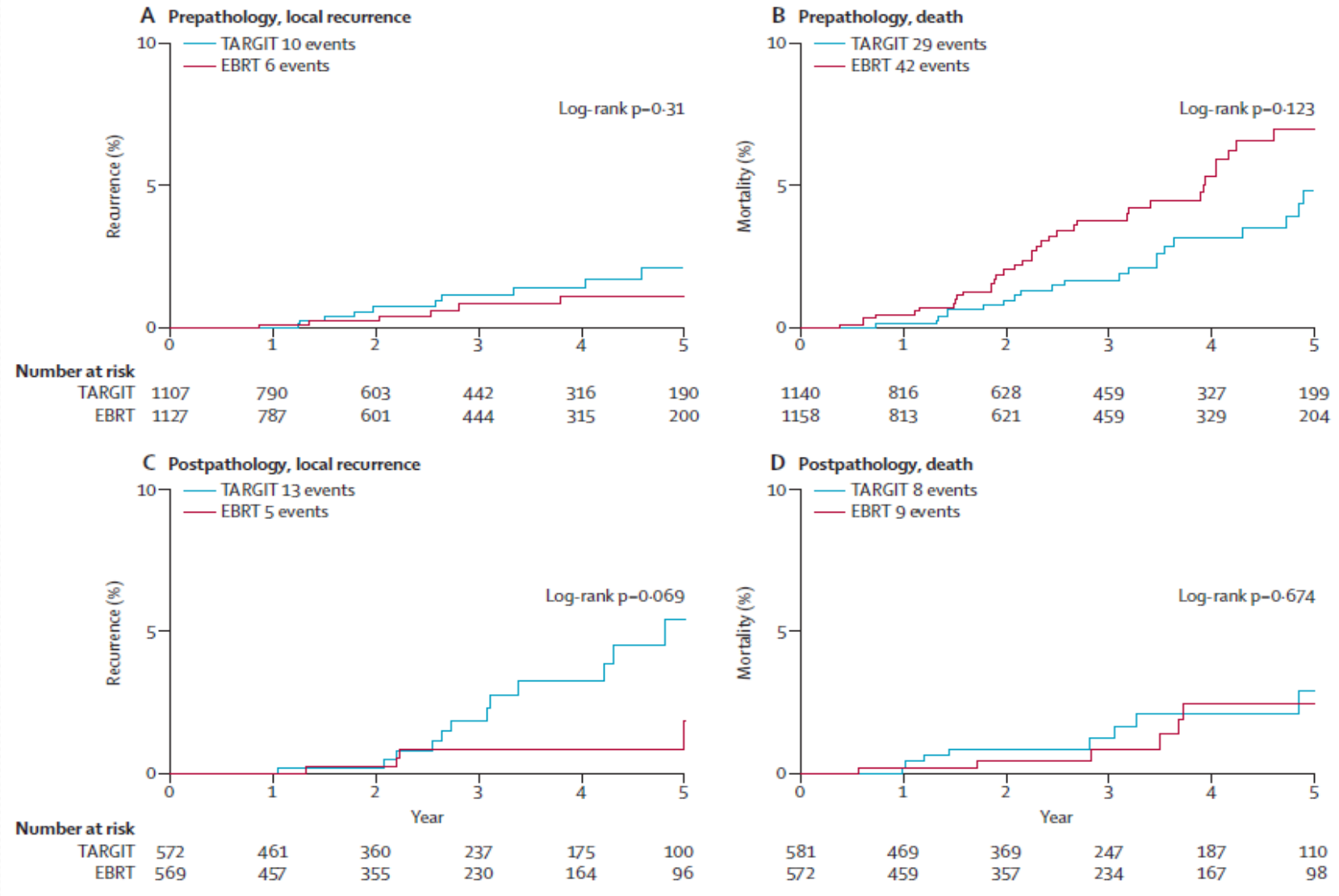
	Events; 5-year cumulative risk (95%CI)		Absolute difference*
	TARGIT	EBRT	
All patients			
Local recurrence (n=3375)	23; 3·3% (2·1–5·1)	11; 1·3% (0·7–2·5)	12 (2·0%)
Any other recurrence (n=3375)	46; 4·9% (3·5–6·9)	37; 4·4% (3·0–6·4)	9 (0·5%)
Death (n=3451)	37; 3·9% (2·7–5·8)	51; 5·3%(3·9–7·3)	−14 (−1·4%)
Prepathology†			
Local recurrence (n=2234)	10; 2·1% (1·1–4·2)	6; 1·1% (0·5–2·5)	4 (1·0%)
Any other recurrence (n=2234)	29; 4·8% (3·1–7·3)	25; 4·7% (3·0–7·4)	4 (0·1%)
Death (n=2298)	29; 4·6% (1·8–6·0)	42; 6·9% (4·3–9·6)	−13 (−2·3%)
Postpathology‡			
Local recurrence (n=1141)	13; 5·4% (3·0–9·7)	5; 1·7%(0·6–4·9)	8 (3·7%)
Any other recurrence (n=1141)	17; 5·2% (3·0–8·8)	12; 3·7% (1·9–7·0)	5 (1·5%)
Death (n=1153)	8; 2·8% (1·3–5·9)	9; 2·3% (1·0–5·2)	−1 (0·5%)


A Breast cancer deaths
TARGIT 20 events
EBRT 16 events
Mortality (%)
10
5
0
Log-rank p=0·56
0
1
2
3
4
5
Years
B Non-breast cancer deaths
TARGIT 17 events
EBRT 35 events
Log-rank p=0·0086
0
1
2
3
4
5
Years
Number at risk
TARGIT 1721 1285 997 706 514 309
EBRT 1730 1272 978 693 496 302
1721 1285 997 706 514 309
1730 1272 978 693 496 302


A Local recurrence
TARGIT 23 events
EBRT 11 events
Recurrence (%)
10
5
0
Log-rank p=0·042
0 1 2 3 4 5
Number at risk
TARGIT 1679 1251 963 679 491 290
EBRT 1696 1244 956 674 479 296


B Regional recurrence
TARGIT 8 events
EBRT 6 events
Recurrence (%)
10
5
0
Log-rank p=0·609
0 1 2 3 4 5
Number at risk
TARGIT 1679 1251 966 683 495 294
EBRT 1696 1243 957 676 481 297


C Death
TARGIT 37 events
EBRT 51 events
Mortality (%)
10
5
0
Log-rank p=0·099
0 1 2 3 4 5
Years
Number at risk
TARGIT 1721 1285 997 706 514 309
EBRT 1730 1272 978 693 496 302


A Prepathology, local recurrence
TARGIT 10 events
EBRT 6 events
Log-rank p=0·31
Recurrence (%)
10
5
0
0 1 2 3 4 5
Number at risk
TARGIT 1107 790 603 442 316 190
EBRT 1127 787 601 444 315 200
B Prepathology, death
TARGIT 29 events
EBRT 42 events
Log-rank p=0·123
Mortality (%)
10
5
0
0 1 2 3 4 5
1140 816 628 459 327 199
1158 813 621 459 329 204
C Postpathology, local recurrence
TARGIT 13 events
EBRT 5 events
Log-rank p=0·069
Recurrence (%)
10
5
0
0 1 2 3 4 5
Year
Number at risk
TARGIT 572 461 360 237 175 100
EBRT 569 457 355 230 164 96
D Postpathology, death
TARGIT 8 events
EBRT 9 events
Log-rank p=0·674
Mortality (%)
10
5
0
0 1 2 3 4 5
Year
581 469 369 247 187 110
572 459 357 234 167 98

Konular

- Akselere parsiyel meme ışınlaması (APBI)
  - Tanım
  - Multikateter APBI
  - Tek giriş brakiterapi cihazı ile APBI
  - Eksternal APBI

- IORT Parsiyel meme ışınlaması
  - Tanım
  - TARGIT
  - **Elektron**

EIO Milano/ELIOT deneyimi

- Doz yükseltme çalışması (Temmuz 1999- Nisan 2000)
- 21 Gy için Faz II Çalışma (Mayıs-Eylül 2000)
- ELIOT vs WBRT randomize çalışma (2000-...)
- Meme ucu koruyucu mastektomi (Mart 2002-...)
- 48 yaş altındakilere "Boost + AWBI" (2004-...)
- Rekürrent-Reirradiye hastalar (2003-...)

- 7000' den fazla vaka
- Yılda ortalama 800 vaka

ELIOT Çalışması Hakkında

- 1999' da dizayn edildi
- O dönemde Parsiyel Meme Işınlaması oldukça yeniydi
- Memede tek doz 21 Gy' in uygulandığı ilk çalışma
- Seçim kriterleri, o dönemde, yok

Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

Umberto Veronesi, Roberto Orecchia, Patrick Maisonneuve, Giuseppe Viale, Nicole Rotmensz, Claudia Sangalli, Alberto Luini, Paolo Veronesi, Viviana Galimberti, Stefano Zurrida, Maria Cristina Leonardi, Roberta Lazzari, Federica Cattani, Oreste Gentilini, Mattia Intra, Pietro Caldarella, Bettina Ballardini

Summary

Background Intraoperative radiotherapy with electrons allows the substitution of conventional postoperative whole breast irradiation with one session of radiotherapy with the same equivalent dose during surgery. However, its ability to control for recurrence of local disease required confirmation in a randomised controlled trial.

Methods This study was done at the European Institute of Oncology (Milan, Italy). Women aged 48–75 years with early breast cancer, a maximum tumour diameter of up to 2·5 cm, and suitable for breast-conserving surgery were randomly assigned in a 1:1 ratio (using a random permuted block design, stratified for clinical tumour size [<1·0 cm *vs* 1·0–1·4 cm *vs* ≥1·5 cm]) to receive either whole-breast external radiotherapy or intraoperative radiotherapy with electrons. Study coordinators, clinicians, and patients were aware of the assignment. Patients in the intraoperative radiotherapy group received one dose of 21 Gy to the tumour bed during surgery. Those in the external radiotherapy group received 50 Gy in 25 fractions of 2 Gy, followed by a boost of 10 Gy in five fractions. This was an equivalence trial; the prespecified equivalence margin was local recurrence of 7·5% in the intraoperative radiotherapy group. The primary endpoint was occurrence of ipsilateral breast tumour recurrences (IBTR); overall survival was a secondary outcome. The main analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01849133.

Findings 1305 patients were randomised (654 to external radiotherapy and 651 to intraoperative radiotherapy) between Nov 20, 2000, and Dec 27, 2007. After a medium follow-up of 5·8 years (IQR 4·1–7·7), 35 patients in the intraoperative radiotherapy group and four patients in the external radiotherapy group had had an IBTR (p<0·0001). The 5-year event rate for IBRT was 4·4% (95% CI 2·7–6·1) in the intraoperative radiotherapy group and 0·4% (0·0–1·0) in the external radiotherapy group (hazard ratio 9·3 [95% CI 3·3–26·3]). During the same period, 34 women allocated to intraoperative radiotherapy and 31 to external radiotherapy died (p=0·59). 5-year overall survival was 96·8% (95% CI 95·3–98·3) in the intraoperative radiotherapy group and 96·9% (95·5–98·3) in the external radiotherapy group. In patients with data available (n=464 for intraoperative radiotherapy; n=412 for external radiotherapy) we noted significantly fewer skin side-effects in women in the intraoperative radiotherapy group than in those in the external radiotherapy group (p=0·0002).

Interpretation Although the rate of IBTR in the intraoperative radiotherapy group was within the prespecified equivalence margin, the rate was significantly greater than with external radiotherapy, and overall survival did not differ between groups. Improved selection of patients could reduce the rate of IBTR with intraoperative radiotherapy with electrons.

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ELIOT Faz III Randomize Çalışma

Artmış lokal rekürrens oranı;

-T2-3

-G3

-ER –

-TNBC

- 2000-2007 yılları arası, 1305 hasta
- Tm boyutu < T1 %85, ER + %90, N1 hasta %21
- N2 hastalara (%5,5) EBRT
- Medyan takip süresi 5,8 yıl

Veronesi et al, Lancet Oncology, 2013

Toksisite

ELIOT LEHINE	ELIOT = EBRT	EBRT LEHINE
Deri eritemi	Deri atrofisi	Klinik yağ nekrozu
Kuru deri	Deri altı fibrozu	Görüntülemede yağ nekrozu
Hiperpigmentasyon	Deri çekilmesi	Keloid oluşumu
Meme ödemi	Ağrı	
Meme kaşıntısı	Yanma	

IORT PBI : Özet

- IORT PBI destekleyen artan kanıt sayısı
- Bu yaklaşıma en uygun hasta populasyonunun belirlenmesi
- Lokal rekürrens riski olan ancak uzak metastaz riski düşük olan hastalarda bu yaklaşım meme koruma başarısını arttırarak faydalı olabilir

Hasta Seçimi

ASTRO

	"suitable"	utionary"	"unsuitable"
Age	≥60 y		<50 y
BRCA1/2	Not present		Present
Tumor size	≤2 cm		>3 cm
T stage	T1		T3 or T4
Margins	Negative by ≥2 mm		Positive
Grade	Any		
LVSI	No		Extensive
ER status	Positive		
Multicentricity	Unicentric only		Multicentric
Multifocality	Clinically unifocal, total size ≤2.0 cm Microscopic multifocality allowed, provided the lesion is clinically unifocal (by PE and MMG/US) and total lesion size (including intervening normal breast parenchyma) is ≤2.0 cm	e 2.1-3.0 cm llowed, provided the lesion is lesion size is 2.1-3.0 cm cm	Clinically multifocal or microscopically multifocal >3 cm in total size
Histology	Invasive ductal or other favorable subtypes		>3 cm
Pure DCIS	Not allowed		>3 cm
EIC	Not allowed		
Associated LCIS	Allowed		pN1, pN2, pN3
N stage	pN0(i^-,i^+)		None performed
Nodal surgery	SN Bx or ALND		If used
Neoadjuvant	Not allowed		

How Do the ASTRO Consensus Statement Guidelines for the Application of Accelerated Partial Breast Irradiation Fit Intraoperative Radiotherapy? A Retrospective Analysis of Patients Treated at the European Institute of Oncology

Maria Cristina Leonardi, M.D.[*,] , Patrick Maisonneuve, Ing.[†], Mauro Giuseppe Mastropasqua, M.D.[‡], Anna Morra, M.D.[*], Roberta Lazzari, M.D.[*], Nicole Rotmensz, M.Sc.[†], Claudia Sangalli, D.M.[§], Alberto Luini, M.D.[§], Umberto Veronesi, M.D.[¶], Roberto Orecchia, M.D.[*,‖]

International Journal of Radiation Oncology*Biology*Physics

Volume 83, Issue 3, 1 July 2012, Pages 806–813

	ASTRO consensus statement		
	Suitable	Cautionary	Unsuitable
Patients	294	691	812
Person-years	1,009	2,416	2,837

ELIOT APBI: ASTRO APBI Konsensus Kılavuzu

5 year rates	Suitable	Cautionary	Unsuitable	p
n	294	698	812	
Ipsilateral in-breast recurrence	**1.5 %**	**4.4 %**	**8.8 %**	**0.003**
Regional nodal failure	1.5 %	1.9 %	1.1 %	0.55
Distant metastases	1.5 %	1.7 %	3.9 %	0.047
Cause specific survival	99.1 %	98.7 %	96.5 %	0.025

Leonardi, IJROBP 2011

GEC-ESTRO

Characteristic	A/low-risk gr candidates f
Patient age	>50 years
Histology	IDC, mucinou medullary, ar
ILC	Not allowed
Associated LCIS	Allowed
DCIS	Not allowed
HG	Any
Tumour size	pT1–2 (≤30 r
Surgical margins	Negative (≥2
Multicentricity	Unicentric
Multifocality	Unifocal
EIC	Not allowed
LVI	Not allowed
ER, PR status	Any
Nodal status	pN0 (by SLN
Neoadjuvant chemotherapy	Not allowed

Characteristic	A/low-risk group – good candidates for APBI	C/high-risk group – contraindication for APBI
Patient age	>50 years	≤40 years
Histology	IDC, mucinous, tubular, medullary, and colloid cc.	–
ILC	Not allowed	–
Associated LCIS	Allowed	–
DCIS	Not allowed	–
HG	Any	–
Tumour size	pT1–2 (≤30 mm)	pT2 (>30 mm), pT3, pT4
Surgical margins	Negative (≥2 mm)	Positive
Multicentricity	Unicentric	Multicentric
Multifocality	Unifocal	Multifocal (>2 cm from the index lesion)
EIC	Not allowed	Present
LVI	Not allowed	Present
ER, PR status	Any	–
Nodal status	pN0 (by SLNB or ALND[a])	pNx;≥pN2a (4 or more positive nodes)
Neoadjuvant chemotherapy	Not allowed	If used

GEC-ESTRO Rehberine Göre Alt Gurup Analizinde Lokal Rekürrens Oranları

	All	GEC-ESTRO GUIDELINES				Ext-RT IEO (Botteri)
		Good candidates	Possible candidates	Contra-indication	Not assessable	
Pati		572 (31%)	268 (15%)	965 (53%)	17	
Per		1838	847	3602		
Per		1979	911	4001		
Loc		7	12	56	1	
5-year r		1.9%	7.1%	7.8%	6.6%	
Luminal A						
Patients	648	206	129	306	7	733
Person-year-DFS	2330	676	396	1231	27	
Loco-regional relapses	8	0	2	6	0	3
5-year rate*	1.7%	0.0%	2.5%	2.4%	0.0%	0.31
Luminal B						
Patients	977	301	122	548	6	1127
Person-year-DFS	3371	954	402	1987	27	
Loco-regional relapses	50	3	10	36	1	15
5-year rate*	7.4%	1.6%	12.4%	9.1%	18.5%	1.13
HER2						
Patients	53	16	1	36	0	118
Person-year-DFS	176	40	0	135	0	
Loco-regional relapses	6	1	0	5	0	6
5-year rate*	17.0%	12.5%	-	18.5%	-	5.69
Triple negative						
Patients	137	47	16	71	3	208
Person-year-DFS	469	161	49	241	19	
Loco-regional relapses	12	3	0	9	0	7
5-year rate*	12.8%	9.3%	0.0%	18.7%	0.0%	2.66
Distant metastases	34	5	1	27	1	
5-year rate*	2.7%	1.4%	0.6%	3.7%	6.6%	
Deaths	47	5	4	38	0	
5-year rate*	3.4%	1.3%	2.2%	4.7%	0.0%	

5y LR %1,9

Sonuçlar Yayın Aşamasında

Milano ELIOT Düşük Risk Grubu

- >60 yaş
- < 2 cm tümör boyutu
- Grade I/II
- ER (+)
- Ki 67 <% 20
- Luminal A
- ≤ 3 (+) LN

GELECEK ELIOT ÇALIŞMASI İÇİN KRİTERLER

ELIOT
22-24 Gy

[Intervention Review]

Partial breast irradiation for early breast cancer

Margot Lehman[1], Brigid E Hickey[2], Daniel P Francis[3], Adrienne M See[2]

[1]Radiation Oncology Unit, Princess Alexandra Hospital, Brisbane, Australia. [2]Radiation Oncology Mater Service, Princess Alexandra Hospital, Brisbane, Australia. [3]Metro North Public Health Unit, Queensland Health, Brisbane, UK

Authors' conclusions

The limitations of the data currently available mean that we cannot make definitive conclusions about the efficacy and safety or ways to deliver of PBI/APBI. We await completion of ongoing trials.

THE COCHRANE COLLABORATION®

Editorial group: Cochrane Breast Cancer Group.
Publication status and date: New, published in Issue 6, 2014.
Review content assessed as up-to-date: 11 April 2014.

APBI tekniklerinin karşılaştırılması zor

- Total doz (20-45 Gy)
- Fraksiyon büyüklüğü (2,67- 21 Gy)
- Fraksiyon sayısı (1-15 fraksiyon)
- Tekniğe bağlı doz **in**homojenitesi
- Total tedavi zamanı (dakika - 3 hafta)
- Tedavi edilen volüm (mm-yarım meme)

BED

Prospektif çalışmaların sonuçlarını beklemeliyiz

Özet: APBI

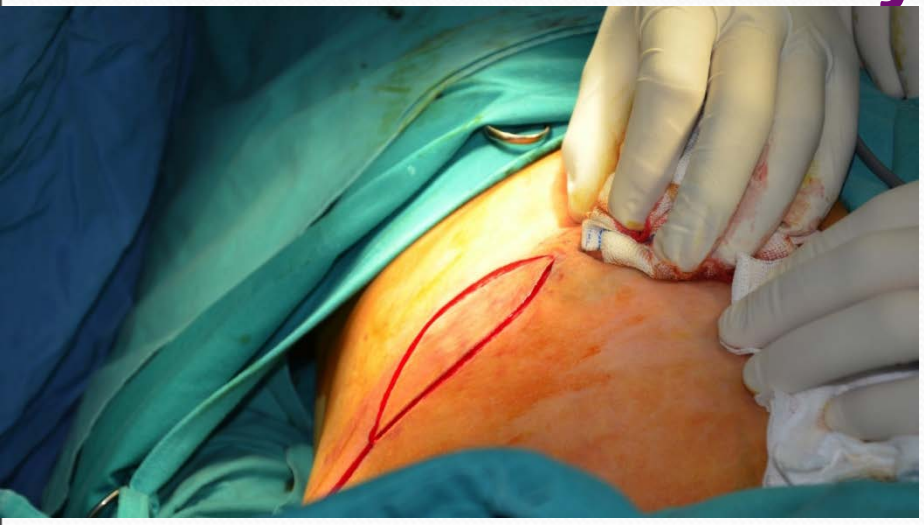
- APBI, seçilmiş, düşük riskli olgularda kabul edilebilir lokal kontrol sağlar
- Sonuçlar küçük çalışmalardan, daha kısa izlem, retrospektif, (seviye 2-3 delil)
- Faz III çalışmalara ihtiyaç var (seviye 1 delil!)
- Faz III çalışmalardan son bilgiler , uygun hasta seçimi+ radyoterapi metodu hala ***net değil*** *(moving target)*
- EBRT ile beraber APBI, intraoperatif metodlar sadece protokol dahilinde yapılmalı
- Hem multikateter hem de intraluminal BRT için kalite kontrolü (QA) ve uygulama tekniğine titizlikle dikkat edilmeli

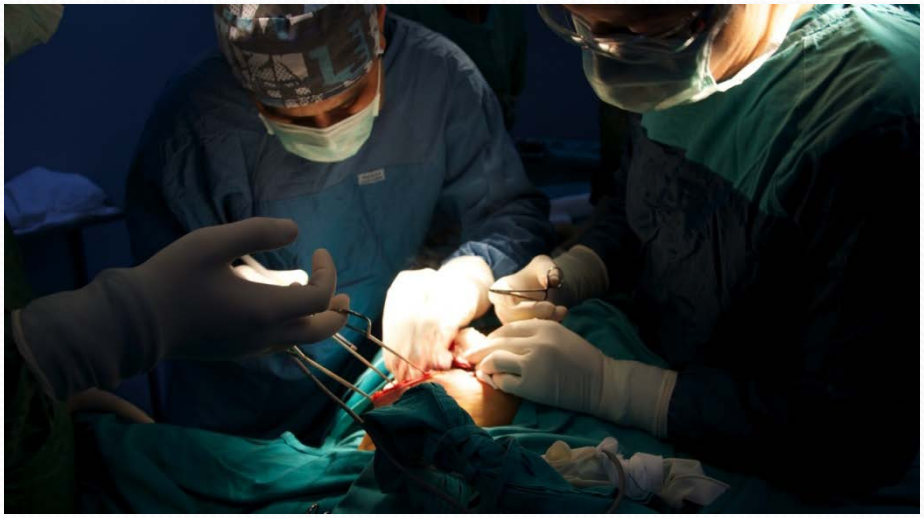
Hasta Seçim Kriterleri GEC-ESTRO

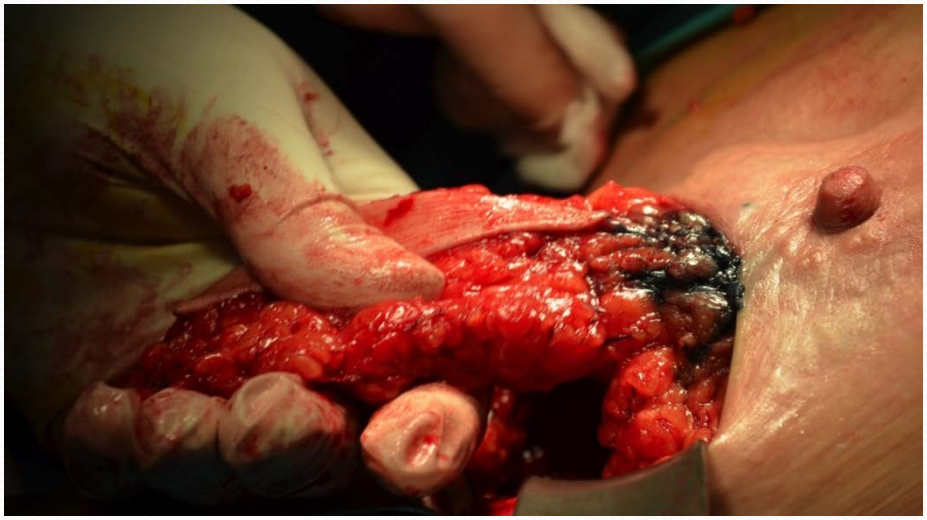
- >50 yaş
- İnvaziv ductal karsinoma
- T<3 cm
- Cerrahi sınır (–)
- Unisentrik ve unifokal
- pNo
- Hormon durumu kriter değil
- Neoadjuvan tedavi (-)

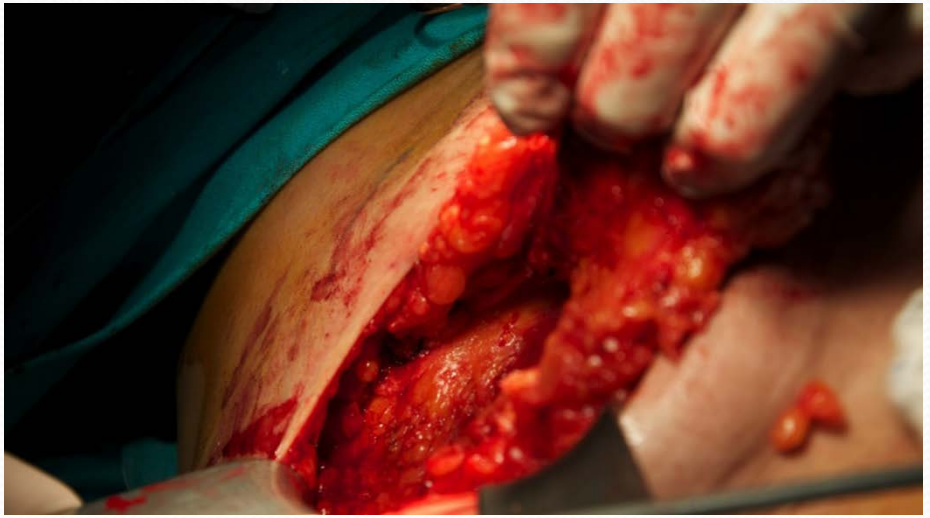
Hareketli LINAK

Ankara Onkoloji Hastanesi

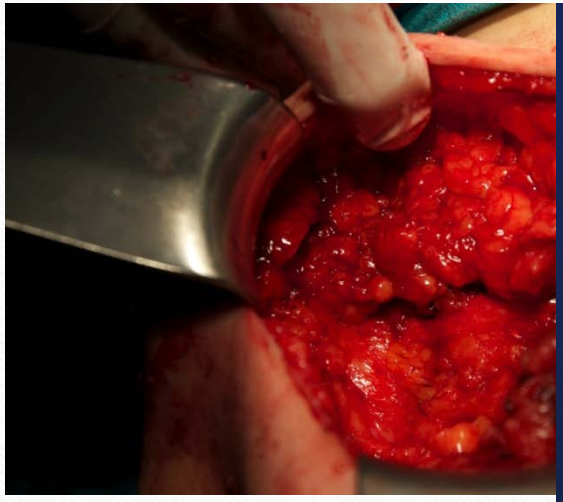


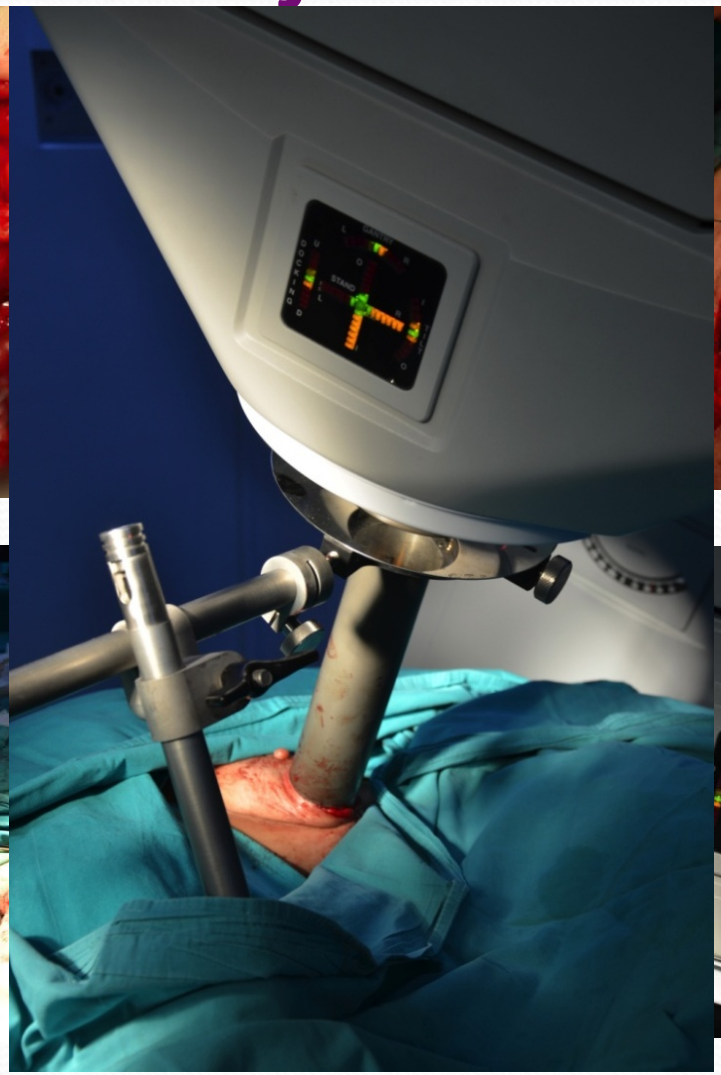


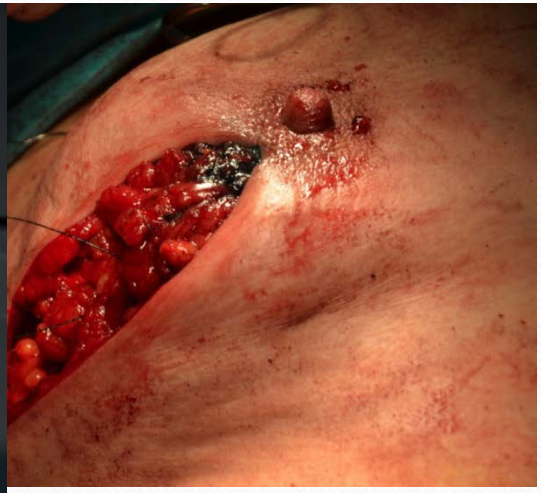


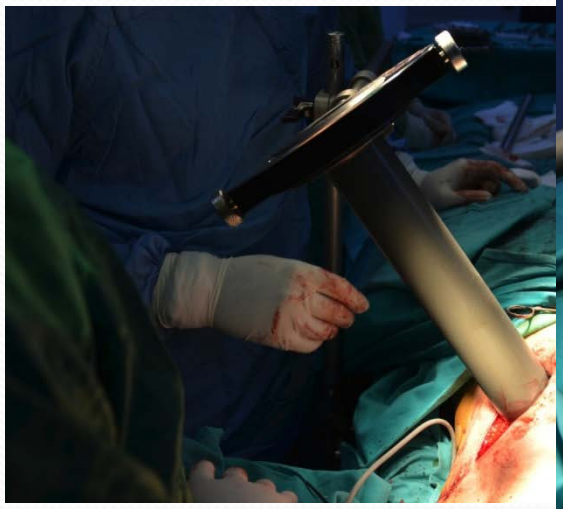


Ankara Onkoloji Hastanesi









AOH IORT DENEYİMİ

EVRELERE GÖRE HASTA SAYILARI

EVRE	HASTA SAYISI
T1c N0	10
T2 N0	5
T1b N1	1
T1c N1	5
T2 N1	2
T1c N2	1
T2 N2	4

Parsiyel meme ışınlaması uygulanan hasta ve özellikleri

Hasta özellikleri	Parametreleri	n=25
Yaş	Ortanca (aralık) 50-60 60+	64 (53-82) 6 (% 29) 19 (% 71)
Tümör bölgesi (kadran)	Üst dış kadran Üst iç kadran Alt dış kadran Alt iç kadran	20 (% 76) 3 (% 14) 1 (% 5) 1 (% 5)
Biyopsi şekli	Eksizyonel Tru-cut	13 (% 57) 12 (% 43)
Tümör çapı (patolojik)	≤ 1 cm 1.1-2 cm >2 cm	7 (% 23.5) 14 (% 57) 4 (% 19)
Histoloji	İDK İnvaziv tübüler karsinom Diğer	20 (% 76) 3 (% 14) 2 (% 10)
Grad	G1 G2 G3 Değerlendirilemeyen	8 (% 33) 9 (% 38) 5 (% 19) 3 (% 10)
Cerrahi sınır (Nihai patoloji)	Negatif Pozitif	23 (% 90) 2 (% 10)
Sentinel lenf nodu (Nihai patoloji)	Negatif Pozitif (mikrometastaz)	23 (% 90) 2 (% 10)
Östrojen reseptörü	Pozitif	25 (% 100)
Progesteron reseptörü	Negatif Pozitif Değerlendirilemeyen	6 (% 24) 18 (% 71) 1 (% 5)
C erbB2 skoru	Skor 0 Skor 1+ Skor 2+ Değerlendirilemeyen	15 (% 71) 2 (% 10) 5 (% 14) 3 (% 5)
Ki-67	≤ % 20 > % 20 Değerlendirilemeyen	17 (% 66) 5 (% 24) 3 (% 10)

G3 olan 4 olgumuzun özellikleri

	Olgu 1	Olgu 2	Olgu 3	Olgu 4
Yaş	65	53	69	82
Tümör çapı (cm)	1,8	1,5	1,5	1,8
ER **PR** **Cerb B2**	+ - - Luminal A	+ + - Luminal A	+ + - Luminal A	+ + - Lumina A

Nihai patolojide tümör çapı 2 cm üzeri olan 4 olgumuzun özellikleri

	Olgu 1	Olgu 2	Olgu 3	Olgu 4
Yaş	63	56	63	64
Tümör çapı (cm)	2,8	2,5	2,5	2,4
Grad	2	2	2	1
ER **PR** **Cerb B2**	+ + - Luminal A	+ - - Luminal A	+ + - Luminal A	+ - - Lumina A
SLN (nihai patoloji)	N1 mik	No	N1 mik	No

Parsiyel meme ışınlaması uygulanan hastaların tedavi özellikleri

Tedavi özellikleri	Parametreleri	n=21
Uygulanan doz	21 Gy	21 (% 100)
Reçete edilen izodoz	% 90 % 95 % 100	19 (% 90) 1 (% 5) 1 (% 5)
Enerji	6 MeV 9 MeV	18 (% 86) 3 (% 14)
Bolus (akrilik disk) kalınlığı	1 cm	21 (% 100)
Bolus (akrilik disk) çapı	Ortanca 6,5 cm Aralık: 5- 9 cm	
Aplikatör çapı	Ortanca 5,5 cm Aralık: 4- 8 cm	
Derinlik	Ortanca 20 mm Aralık: 14- 30 mm	
Monitör Unit (MU)	Ortanca 1641 MU Aralık: 1463- 1973 MU	
Tedavi süresi (dakika)	Ortanca 2,04 dk Aralık: 1,26- 2,44 dk	
Adjuvan- sistemik tedavi	Sadece hormonoterapi Hormonoterapi+kemoterapi Takip dışı	11 (% 52) 9 (% 43) 1 (% 5)

Parsiyel meme ışınlaması uygulanan hastalarda görülen akut ve geç toksisite

Akut Toksisite	n=8
Seroma	4
Mastit	1
Abse	1
Enfekte açık yara	2
Geç Toksisite	**n=13**
Mastit	1
Abse	1
Yağ nekrozu	3
Fibrozis	3
Memede ağrı	5

Parsiyel meme ışınlaması sonrası hasta ve doktora göre kozmetik sonuçlar

	Doktor	Hasta
Kozmetik sonuç	**n=19**	**n=19**
Mükemmel	6 (% 32)	4 (% 21)
İyi	9 (% 47)	14 (% 74)
Orta	4 (% 21)	1 (% 5)
Kötü	0	0

PARSİYEL MEME RADYOTERAPİSİ HASTA ALIM KRİTERLERİ

TROD Meme Çalışma Grubu

1. Lumpektomi yapılan hastalar
2. ≥50 yaş
3. T≤2 cm
4. pN0 olgular (Aksillerevreleme yapılmış olmalıdır)
   1. SLN (-)
   2. SLND'da izole tümör hücresi varlığı
   3. AD yapılmış ise pN0 (yeterli AD: 10LN)
5. İnvaziv duktal karsinom ya da diğer iyi histopatolojik alt tipler (müsinöz, tübüler, medüller ya da kolloidkarsinom)

PARSİYEL MEME RADYOTERAPİSİ HASTA ALIM KRİTERLERİ

TROD Meme Çalışma Grubu

6. İlişkili LCIS olabilir
7. Cerrahi sınırları negatif olan olgular (≥2 mm)
8. Grade 1 ya da 2
9. Lenfovasküler boşluk invazyonu olmayan olgular
10. Unisentrik tm
11. Klinik unifokal tm
12. Luminal A olgular: ER (+) ve Ki 67 <%14
13. CerbB2 (-)
14. Aile öyküsünde 1. ve 2. derece yakınlarında premenapozal meme kanseri öyküsü olmayan olgular

PARSİYEL MEME RADYOTERAPİSİ HASTA ALIM KRİTERLERİ

TROD Meme Çalışma Grubu

15. Postoperatif dönemde RT öncesi çekilen BT görüntülemede hedef lumpektomikavitesi net olarak değerlendirilebilmeli ve hedef lumpektomikavitesi/tüm meme referans hacmi oranı ≤%30 olmalıdır.

16. Cerrahi öncesi MMG-USG ve gereken olgularda meme MRG çekilmeli. Postop.spesmen MMG özendirilmeli. Kuşkulu olgularda cerrahi sonrası MMG/USG tekrarlanmalı.

17. Meme kanseri dışında malignansi hikayesi olan (insituserviks kanseri, insitu kolon kanseri, melanomainsitu, cilt BCC ve SCC) ve son 5 yıldır hastalıksız olan olgular çalışmaya dahil edilebilir.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